Rethinking interhemispheric imbalance as a target for stroke neurorehabilitation

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Abstract: OBJECTIVE Patients with chronic stroke have been shown to have failure to release interhemispheric inhibition (IHI) from the intact to the damaged hemisphere before movement execution (premovement IHI). This inhibitory imbalance was found to correlate with poor motor performance in the chronic stage after stroke and has since become a target for therapeutic interventions. The logic of this approach, however, implies that abnormal premovement IHI is causal to poor behavioral outcome and should therefore be present early after stroke when motor impairment is at its worst. To test this idea, in a longitudinal study, we investigated interhemispheric interactions by tracking patients' premovement IHI for one year following stroke. METHODS We assessed premovement IHI and motor behavior five times over a 1-year period after ischemic stroke in 22 patients and 11 healthy participants. RESULTS We found that premovement IHI was normal during the acute/subacute period and only became abnormal at the chronic stage; specifically, release of IHI in movement preparation worsened as motor behavior improved. In addition, premovement IHI did not correlate with behavioral measures cross-sectionally, whereas the longitudinal emergence of abnormal premovement IHI from the acute to the chronic stage was inversely correlated with recovery of finger individuation. INTERPRETATION These results suggest that interhemispheric imbalance is not a cause of poor motor recovery, but instead might be the consequence of underlying recovery processes. These findings call into question the rehabilitation strategy of attempting to rebalance interhemispheric interactions in order to improve motor recovery after stroke. Ann Neurol 2019;85:502-513.

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Rethinking interhemispheric imbalance as a target for stroke neurorehabilitation

Running head: No interhemispheric imbalance early after stroke

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Abstract

OBJECTIVE: Patients with chronic stroke have been shown to have failure to release interhemispheric inhibition from the intact to the damaged hemisphere prior to movement execution (*pre-movement-IHI*). This inhibitory imbalance was found to correlate with poor motor performance in the chronic stage after stroke, and has since become a target for therapeutic interventions. The logic of this approach, however, implies that abnormal pre-movement-IHI is causal to poor behavioral outcome, and should therefore be present early after stroke when motor impairment is at its worst. In a longitudinal study, we investigated interhemispheric interactions by tracking patients' pre-movement-IHI for one year following stroke.

METHODS: We assessed pre-movement-IHI and motor behavior five times over a one-year period after ischemic stroke in 22 patients, and in 11 healthy participants.

RESULTS: We found that pre-movement-IHI was normal during the acute/subacute period, and only became abnormal at the chronic stage; specifically, release of IHI in movement preparation worsened as motor behavior improved. In addition, pre-movement-IHI did not correlate with behavioral measures cross-sectionally, while the longitudinal emergence of abnormal pre-movement-IHI from the acute to the chronic stage was inversely correlated with recovery of finger individuation.

INTERPRETATION: These results suggest that interhemispheric imbalance is not a cause of poor motor recovery but instead might be the consequence of underlying recovery processes. These findings call into question the rehabilitation strategy of attempting to rebalance interhemispheric interactions in order to improve motor recovery after stroke.

Keywords: stroke recovery, interhemispheric inhibition, movement preparation

Introduction

It has been proposed that one contributor to chronic hemiparesis is an imbalanced inhibitory interaction between the lesioned and intact hemispheres via transcallosal connections. This *interhemispheric-competition model* proposes that the two hemispheres, which normally exert mutual inhibition in healthy individuals, become imbalanced after stroke, and that unopposed inhibition from the healthy to the damaged side impedes recovery[1]. This framework is largely based on a seminal study that showed persistent pre-movement interhemispheric-inhibition (IHI) from the contra- to ipsi-lesional motor cortex prior to movement execution in patients with chronic stroke[2]. This failure to release IHI prior to movement onset (abnormal *pre-movement-IHI*) correlated with weakness and impaired finger tapping performance[2]. Influenced by this stroke-recovery model, numerous studies in the neurorehabilitation field have used different approaches (e.g. brain stimulation, peripheral stimulation, and transient deafferentation) in an attempt to down-regulate excitability in the unaffected hemisphere and thus rebalance putative abnormal interhemispheric-inhibition (see recent studies[3,4] and reviews[5–7]).

The problem with the interhemispheric-competition model is that abnormal pre-movement-IHI has only been described in patients with chronic stroke and relatively mild impairment. Stinear and colleagues[8], using an indirect measure of IHI, recently found no evidence for hemispheric-imbalance in the first three months after stroke. To date it remains unclear if imbalanced interhemispheric interactions are present in the context of movement early after stroke, whether they evolve over time, and if they have any predictive value for motor recovery. If interhemispheric interactions are normal early after stroke, then designing rehabilitation strategies based on the interhemispheric-competition model is questionable. Here in a longitudinal observational study of patients with mild-to-moderate hemiparesis, we

investigated the evolution of pre-movement-IHI over the first year after stroke and related it to motor recovery of the hand. To this end, we followed the same inclusion-exclusion criteria and procedures as the seminal study of Murase and colleagues[2].

Methods

Participants

Twenty-two patients with hemiparesis from first-time ischemic stroke (7 female; mean-age 57.5±16 years, 15 right-handed according to the Edinburgh Handedness Inventory[9]) were recruited from three centers (The Johns Hopkins Hospital and Affiliates (JHM), Columbia University Medical Center (CU), and The University Hospital of Zurich & Cereneo Center for Neurology and Rehabilitation (UZ)) for a prospective cohort study over the course of four years. All patients met the following inclusion criteria: 1) First-ever ischemic stroke confirmed by MRI within the previous 2 weeks; 2) One-sided upper extremity weakness (MRC<5). We excluded patients with the following criteria: contraindications to magnetic stimulation, age under 21 years, hemorrhagic stroke, space-occupying hemorrhagic transformation, bilateral hemiparesis, traumatic brain injury, encephalopathy, global inattention, visual-field cut larger than a quadrantanopia, receptive aphasia, inability to give informed consent or understand the tasks, major neurological or psychiatric illness that could confound performance/recovery, or a physical or other neurological condition that would interfere with arm, wrist, or hand function recovery. See Table 1 for details of patient characteristics.

We also recruited 11 age-matched healthy control participants (4 female; mean age 64±9 years; all right-handed) at the three centers. All participants gave written consent and the respective Institutional Research Board at each study center approved all procedures. All

procedures were in compliance with the Declaration of Helsinki. All patients were tested at five time points over one-year period (Table 2).

Table 1

Assessment of Interhemispheric Inhibition with Transcranial Magnetic Stimulation (TMS)

TMS procedures and IHI assessments. Participants were comfortably seated in an armchair, arms resting on a pillow and faced a computer monitor. IHI was assessed by a double-pulse paradigm[2,10] (Fig 1A), with two figure-of-eight coils (diameters of wings 70mm and 50mm), each connected to a Magstim-200 magnetic stimulator (Magstim, UK). The larger coil was placed tangentially over the lesioned M1 (for testing stimulus, TS), with the handle oriented toward the back of the head and laterally at a 45º angle from the midsagittal line. The smaller coil was oriented perpendicular to midsagittal line over the unaffected M1 (for conditioning stimulus, CS). For healthy age-matched controls, the CS was always applied to the right M1 and the TS to the left M1, contralateral to the moving right hand. The positions of the coils on the skull were adjusted to produce a maximal response in the contralateral first dorsal interosseus (FDI) muscles (the hotspots). A frameless stereotactic neuronavigation device (Brainsight, Rogue Research Inc, CA) was used to track coil positions within and across sessions.

Two stimulation conditions were used to calculate IHI: *non-conditioned* trials (NC: TS-only), where only a TS pulse was delivered, and *conditioned* trials (C: CS+TS), where a CS pulse was delivered prior to a TS pulse with an inter-stimulus interval (ISI) of 10ms. Conditioned and unconditioned trials were intermixed and randomized throughout the testing session.

IHI was assessed in two contexts: at rest (resting) and during movement preparation (pre-movement). Following a previous study, IHI at rest was obtained in order to determine the stimulation parameters for pre-movement-IHI[2]. For resting-IHI, intensities of TS and CS were first set at the minimum maximal-stimulator-output (MSO) that produced a contralateral motor-evoked-potential (MEP) with amplitude 0.5-1mV. The CS intensity was then adjusted to produce a ~50% reduction in TS-MEP amplitude. The resting-IHI assessment consisted of a block of 36 trials with 18 each for NC and C stimulation.

During the pre-movement-IHI task, while the participant performed a simple reaction-time (RT) task, a TMS pulse was then delivered on each trial at four possible epochs: 20, 50, 80, and 95% of each participant's RT (see the section below, Fig. 1B). The TS intensity was determined in the same way as for resting-IHI. To assess the CS-intensity in the context of movement execution, participants were asked to perform the same RT task when double-TMS pulses were delivered at an estimated 50% of RT on each trial, and CS-intensity was adjusted to the level approximating 50% of the TS-MEP. This adjustment was to probe the largest possible dynamic range of CS modulation during pre-movement-IHI testing. As described previously[2], when probed at different times during the RT, a healthy control's typical IHI curve shows an initial reduction, followed by increases of MEP when stimulation is delivered closer to movement onset, i.e. interhemispheric-inhibition switches to facilitation (release-of-inhibition).

A total of six blocks, with 24 pre-movement-IHI trials per block, were run in each testing session, with 18 pulses per stimulation/time-epoch condition. Sessions were not run if patients could not abduct their index finger or if the stimulation intensity was too high to obtain both resting- and pre-movement-IHI (required ≥90 MSO to elicit an MEP >0.5mV). These patients were still included in the study if IHI could be obtained in subsequent visits.

Resting motor threshold (rMT) for both FDIs were determined as the minimal TMS intensity required to evoke MEPs of ~50μV (peak-to-peak amplitude) in the targeted muscle on five out of ten consecutive trials.

Because MEP amplitudes increase in the moving effector immediately before movement onset, leading to large MEP that can mask the true size of release-of-inhibition (or contralateral facilitation), we compared the MEP amplitudes recorded during the pre-movement-IHI procedure with maximal amplitudes obtained in each participant using assessment of active corticospinal tract (aCST). This was done with 18 single pulses delivered at 100% MSO with an inter-stimulus interval (ISI) of 5-7s, while the participant was actively contracting the contralateral FDI at a constant level of 20% of their maximum voluntary contraction force.

EMG recording. Electromyogram (EMG) activity was monitored from surface electrodes placed over the FDI in both hands. Three EMG systems were used at the three sites: SX230-100 and K800, Biometrics Ltd. (CU); AMT-8; Bortec Biomedical Ltd. (JHM); and Telemyo desk receiver, Noraxon (UZ). The Biometrics EMG signal was sampled at 1000Hz, amplified 1000x, band-pass filtered at 15-450Hz; the AMT-8 EMG signal was sampled at 1000Hz, amplified 1000x, band-pass filtered at 10-1000Hz; and the Noraxon EMG was sampled at 1500Hz, amplified 500x, band-pass filtered at 15-450Hz. EMG signals were used to determine RTs and MEP amplitudes (see ***Measures of pre-movement-IHI*** section).

Figure 1

Simple reaction-time task for pre-movement-IHI assessment

Pre-movement-IHI was assessed while participants performed a simple RT task. The participants were instructed to make a voluntary index-finger abduction in response to a GO-cue (green dot). Patients used their paretic hand, while healthy volunteers always performed the task with their right hand. The GO-cue was displayed on the monitor for 2 seconds, and disappeared at the end of the trial. The inter-trial interval (ITI) was 5 seconds plus 0-2 seconds of jitter to prevent anticipation.

Prior to the IHI procedure, each participant performed the simple reaction task for 30 trials to determine their average RT. The last 15 trials were used to calculate the RT.

Stroke-related behavioral assessments

All patients' and controls' upper-extremity motor impairment was determined with the Fugl-Meyer assessment (FMA)[11], following the same schedule as pre-movement-IHI. Hand function was also tested within ±4.6 days from the TMS experiment, as previously described[12]. Briefly, participants were instructed to move each finger in isolation on an ergonomic device that measures the isometric force generated by each digit. A Strength Index was calculated from the maximum voluntary force (MVF) of individual finger flexion, normalized to the MVFs on the non-paretic side at one-year time point. An Individuation Index was derived from the activation in the non-instructed fingers as a function of force produced by the instructed finger pressing to 4 levels of target forces.

Measures of pre-movement-IHI

EMG was used to measure RT and peak-to-peak amplitudes of the MEPs elicited in FDI of both hands. Both RTs and MEPs were identified using custom-made MATLAB scripts (The MathWorks, Inc., Natick, MA) from the EMG recordings. The RT was manually identified with

208 the following criteria: peak-to-peak waveforms of EMG activity >100μV and lasting longer than
209 50ms following the GO-cue.

210 The following trial types were excluded from further analysis: 1) Trials with any
211 background EMG activity >20μV in the 150ms window preceding the TMS pulse in either FDI;
212 2) MEP size <50μV; 3) MEP occurrence after movement onset; 4) RT >1000ms. An analysis of
213 the background pre-trigger EMG across different TMS epochs was also conducted to rule out the
214 potential influence of systematic differences in background EMG on the pre-movement-IHI
215 results.

216 Resting and pre-movement-IHI was computed as the ratio C/NC. An IHI-ratio of 1
217 indicates no interhemispheric-inhibition. To prevent averaging epochs with too few MEP
218 observations, a minimum of 9 good MEPs (1/2 of the total count) was required to compute the
219 ratio. A good TS-MEP was defined as: 1) No background EMG activity in the 150ms window
220 before the TMS pulse; 2) The MEP occurred before movement onset; 3) Peak-to-peak amplitude
221 was >50μV; 4) Distinct movement is detectable (EMG>100μV for >50ms) within 1000ms after
222 GO-cue. TMS timing epochs with <9 good MEPs were counted as missing values. To evaluate
223 the reproducibility of the IHI-ratio as the main dependent variable in this study, we computed its
224 Cronbach's alpha[13,14]. Mathematically, alpha is equivalent to the averaged split-half correlation
225 of all possible splits of the existing data: $\alpha = \frac{1}{N_{all\ splits}} \sum_{i=1}^{N_{all\ splits}} r_i$.

226 To assess the evolution of IHI during movement preparation, we derived three other
227 measures: $IHI_{EARLY-EPOCH} = mean(IHI_{20\%RT}, IHI_{50\%RT})$, $IHI_{LATE-EPOCH} = mean(IHI_{80\%RT}, IHI_{95\%RT})$,
228 and $\Delta IHI = IHI_{LATE-EPOCH} - IHI_{EARLY-EPOCH}$. ΔIHI therefore reflects the amount of release-of-
229 interhemispheric-inhibition during movement preparation. A value of ΔIHI=0 indicates no

modulation of inhibition[15]; while a positive value implies a release-of-inhibition during movement preparation. Hereinafter, we will use *ΔIHI* as an operational definition of *pre-movement-IHI* to refer to the level of release-of-inhibition prior to movement onset.

Statistical analysis

Data analysis was done with custom-written MATLAB and R (R Core Team, 2017) routines. Given that there were missing sessions (on average, each patient completed 3.4 sessions and each healthy control completed 3.5 sessions, out of a total of 5), we used two analysis approaches: 1) For the primary analysis, we assumed missing *ΔIHI* values arose at random (MAR), and used linear mixed-effects models implemented in the *lme4* package in R[16] to test for changes in the neurophysiology and behavioral measures over time, with a random-factor of Subject, and fixed-factors of Time-Point (five time-points from W1-W52, or acute/subacute vs. chronic), Hand-Condition (paretic, non-paretic, and/or control), and/or TMS-Epoch (early vs. late TMS timing). 2) Because there are cases where data were missing due to severity of impairment, specifically when there was no reliable finger abduction and/or MEP at a given assessment session, there was a concern about the possibility of a systematic relationship between pre-movement-IHI and missingness. We therefore conducted a sensitivity analysis by imputing missing values under different data-generating mechanisms. Specifically, we implemented the assumptions of either no-dependency or strong-dependency between pre-movement-IHI and the severity of initial impairment (Figure 3D-E). No-dependency mimics the MAR assumption of the mixed-model, with imputed samples drawn from $N\sim(\mu_{(t,patient)}, \sigma_{(t,patient)})$, where $\mu_{(t,patient)}$ and $\sigma_{(t,patient)}$ are estimated from patient data at each time point; while strong-dependency represents a scenario in which severely affected patients have *ΔIHI* values centered at 0, with imputed samples from $N\sim(0, \sigma_{patient})$, where $\sigma_{patient}$ is estimated from all patients' data.

For each dataset containing imputed values, we fit the linear mixed-model as specified above. ANOVA tests for sensitivity analyses were conducted by pooling significance tests of multiply-imputed datasets[17].

For behavioral results, we included all available behavioral data, including the sessions in which we could not obtain IHI.

Results

We tested a total of 22 patients from the acute to chronic stages after stroke and 11 healthy controls. Each participant was expected to undergo five testing sessions over the course of a one-year period. One patient appeared to meet initial inclusion criteria, but was later found to have bilateral strokes and was excluded from further analysis. The final analysis included a total of 110 pre-movement-IHI sessions from 21 patients and 11 controls. Thirteen patients and 8 controls completed ≥3 sessions. The distributions of assessment time and missing data are presented in Table 2. Non-tested sessions were treated as missing data and all available data were used in the statistical analyses. The data showed good reliability for the major dependent variable, IHI-ratio, for both patients and controls (α=0.74 and 0.79 for patients and controls; Methods). Figure 2 shows the distribution of lesions defined using Diffusion Tensor Images (details reported in our earlier publication[12]).

Figure 2 and Table 2

Pre-movement-IHI changed from normal to abnormal as paresis improved from the acute to the chronic stage

Our main goal was to determine how IHI prior to movement onset evolves over the first year after stroke and how this relates to motor recovery. Figure 3A shows a representative patient's IHI curves at the acute/subacute and chronic stages, as compared to a healthy age-matched control. Figure 3B-C show the group data for controls and patients. Visual inspection of these curves suggests that, consistent with the previous report by Murase and colleagues[2], patients in the chronic stage had an abnormal IHI pattern, characterized by the absence of release-of-inhibition at movement onset. Crucially, however, in the acute/subacute period (W1-12) release-of-IHI at movement onset in patients did not appear to differ from controls. Specifically, the IHI-ratio at weeks 1-12 post-stroke increased over the movement-preparation interval, approaching a ratio of 1 at later stimulation epochs (80-95% RT), indicating a level of release-of-inhibition prior to movement onset similar to healthy controls.

Given that in previous reports, and corroborated here, the post-stroke abnormality in pre-movement-IHI is most apparent at movement onset, our statistical analyses focused on *ΔIHI*, as in prior studies[15,18]. *ΔIHI* is the difference between $IHI_{LATE\text{-}EPOCH}$ and $IHI_{EARLY\text{-}EPOCH}$, which captures the level of release-of-IHI immediately prior to movement onset (Methods). An ANOVA using a mixed-effects model for *ΔIHI* yielded a significant Week × Group (patients vs. controls) interaction (χ^2=4.59, p=0.03). The evolution of *ΔIHI* from the acute/subacute to the chronic stage after stroke clearly showed that at earlier stages (W1-12), patients and controls were similar ($t(21) = 0.50,\ p = 0.62$), while the two groups started to diverge from W24 onward ($t(31) = 3.30,\ p = 0.0025$) (Fig. 3D). Our sensitivity tests also indicate that this trend is robust to the differences in the data-generating mechanisms considered (p=0.028 for MAR and p=0.10 for informed missingness, Fig. 3D-E, Methods). To directly compare *ΔIHI* in the acute versus the chronic stage, we pooled data into two Time-periods: mean(W1-12) (acute/subacute for patients)

and mean(W24-52) (chronic for patients). This data pooling was further supported by our observation that there was no difference in patients' *ΔIHI* from W1-12 (p=0.17), or from W24-52 (p=0.70). The mixed-effects model with Time-period and Group (patients vs. controls) as fixed factors showed a significant interaction (χ^2=6.68, p=0.01). These results show that patients' pre-movement-IHI progressed from normal in the acute/subacute period to abnormal in the chronic stage in the case of mild-to-moderate paresis.

Figure 3

The development of abnormal pre-movement-IHI was inversely correlated with the extent of finger individuation recovery

Our cohort of patients was mild-to-moderately impaired in the acute stage ($FMA_{INITIAL}$ Mean = 41±22, Table 1). Motor recovery was quantified using three behavioral measures: FMA, Strength and an Individuation Index for finger (ability to move digits independently; Methods)[12]. All three measures showed good early recovery (Strength: χ^2=28.07, p<.001, Individuation: χ^2=13.64, p<0.001, and FMA: χ^2=28.07, p<.001), but then plateaued after the subacute stage (Fig 3).

Figure 4

We then sought to determine if there was any correlation between abnormal pre-movement-IHI and motor behavior. To address this question, we first examined the cross-sectional correlation between *ΔIHI* and all three behavioral measures at both the acute/subacute

and chronic stages; none of the correlations were significant with the null value (0) lying within 95% *CI*'s (Table 3). Thus there was no clear relationship between abnormal pre-movement-IHI with strength, individuation, or motor impairment at any time point.

Table 3

Both the opposite longitudinal time-courses for motor recovery and development of abnormal pre-movement-IHI, and the lack of significant cross-sectional correlation between the two, suggest that the pre-movement-IHI abnormality was not causally related to behavioral impairment. Instead, the emergence of abnormal pre-movement-IHI (failure-to-release inhibition during movement preparation) may be a marker for underlying recovery processes (see Discussion). To address this alternative possibility, we examined the correlation between longitudinal motor-function recovery (change in behavior) and the emergence of the failure-to-release IHI (reduction in *ΔIHI*) from the acute/subacute to the chronic stages. We found a strong negative correlation between the reduction of *ΔIHI* and the amount of improvement in the Individuation Index (r=-0.73, p=0.003, 95% *CI*: [-0.91, -0.33]). This suggests that the emergence of failure-to-release IHI during movement preparation and poor finger-individuation recovery share a latent cause. We did not find a significant correlation between changes in *ΔIHI* and changes in the Strength Index (r=0.22, p=0.44, 95% *CI*: [-0.35, 0.67]; Fig. 5). This observation is consistent with the fact that by week 52 at the group level, patients' strength was not far from healthy levels ($t(26)$=1.43, p=0.16), but finger individuation was ($t(26)$=2.43, p=0.02).

Figure 5

345 ----------

346 ***Other TMS and behavioral measures***

347 In addition to pre-movement-IHI, we also measured the participants' rMT, aCST, and
348 resting-IHI for the FDI muscle (Methods). Results from these measures are reported in Table 4.
349 Consistent with the previous literature[2,19], IHI_{REST} in patients and controls did not differ. Patients
350 and controls had comparable TS- and CS-stimulation intensities for both resting- and pre-
351 movement-IHI. For rMT, we included sessions when pre-movement-IHI was not obtainable, and
352 consistent with prior reports[8,20], the results showed higher rMT on the lesioned hemsphere,
353 reflecting lower level of M1 output at acute-subacute stages in severely-impaired patients.

354 To ensure our pre-movement-IHI results were not due to high MEP amplitudes,
355 especially during the later TMS-epochs, we compared the MEP sizes obtained from aCST with
356 the single-pulse TS at late TMS epochs (80 and 95% RT; Methods). If TS-MEPs approach the
357 MEP amplitudes of the aCST, when MEP amplitudes are expected to be near-maximal, the
358 amount of IHI modulation during movement preparation could lack sufficient dynamic range or
359 be masked. We found, however, that most late-epoch MEP amplitudes were lower than those
360 obtained during the aCST assessment (see statistics in Table 4).

361 ----------

362 Table 4

363 ----------

364 It might be posited that one way that failure-to-release inhibition might influence
365 behavior is to prolong the RT. We therefore examined the relationship between the RT and pre-
366 movement-IHI in the simple RT task. RTs in patients were prolonged compared to controls (Fig.
367 6A-B, χ^2=9.19, p=0.002), but this prolongation was not linked to changes in pre-movement-IHI:

there was no interaction with *ΔIHI* and RT (χ^2=0.31, p=0.58).

To rule out the possibility of background EMG influencing the observed pre-movement-IHI patterns, we also performed a mixed-effect model analyses on pre-trigger EMG (Methods). Results showed that background EMG was higher in healthy controls (χ^2=5.46, p=0.019), and decreased over time in both groups (χ^2=45.23, $p=1.77 \times e^{-11}$), possibly due to participants becoming more acquainted with the testing procedure (Fig. 6C-D). Critically, there was no main effect of conditioned (C) vs. non-conditioned (NC) trials, nor any interaction between group and any other factor. Thus, differences in background EMG cannot explain the pre-movement-IHI findings.

Finally, age did not influence the main dependent variable *ΔIHI* (χ^2=0.53, p=0.47), nor did it interact with Week (χ^2=4.73, p=0.09). Similarly, age also did not modulate the behavioral outcome variables in our cohort: Strength, Individuation, FMA, and ARAT.

Figure 6

Discussion

In a longitudinal multi-center study, we tracked the evolution of pre-movement-interhemispheric-inhibition (IHI) from stroke onset up to one year. We used a double-pulse TMS paradigm to test patients and healthy controls at five time-points: week 1, 4, 12, 24, and 52. We also tracked patients' finger strength and individuation, and overall motor impairment (FMA). We found that release-of-IHI prior to movement onset was normal in the acute/subacute period, and became abnormal in the chronic stage. Conversely, behavioral outcomes were most impaired

391 in the acute/subacute period and improved over time to reach plateau in the chronic stage. In
392 addition to these opposite longitudinal trends for the physiological and behavioral measures, we
393 found no significant cross-sectional correlations between pre-movement-IHI and behavioral
394 measures in the patients (strength and individuation). The only significant correlation was an
395 inverse relationship between the development of abnormal pre-movement-IHI from the
396 acute/subacute to the chronic stage after stroke (i.e., the emergence of the failure-to-release IHI
397 prior to movement onset) and the amount of recovery in finger individuation across the same
398 time period.

399 In the seminal study by Murase and colleagues[2], impaired pre-movement-IHI was found
400 in nine patients with chronic stroke. This study has become highly influential and, in our view,
401 was prematurely interpreted by the overall neurorehabilitation field as suggesting a possible
402 causal relationship between IHI and recovery of motor impairment. This interpretation is
403 problematic because: A) Pre-movement-IHI is only one kind of inter-hemispheric measure; it is
404 possible to assess interhemispheric-inhibition at other inter-stimulus intervals or
405 interhemispheric-facilitation[21]. B) Pre-movement-IHI is only obtainable in patients with
406 detectable MEPs and finger movements; it cannot be assessed in patients with more severe motor
407 deficits. C) The study by Murase and colleagues had a small sample of patients at only one time-
408 point in the chronic stage, which makes inference about changes over time, or recovery,
409 impossible. The over-interpretation of the Murase et al. results led in turn to a large number of
410 studies that attempted, or claimed, to rebalance IHI using non-invasive brain stimulation (NIBS)
411 in the acute and chronic stages after stroke[22–26]. What should have been established first, in our
412 view, is the time-course of the development of pre-movement-IHI abnormality from the
413 acute/subacute period to the chronic stage.

The critical finding reported here is that in the acute/subacute period, in those patients that could be assessed with this TMS technique, we found *normal* modulation of pre-movement-IHI despite their motor deficits. Failure-to-release pre-movement-IHI only emerged in the chronic stage, whereas the behavioral measures all improved over the same time period. This contrast makes any claim to a causal relationship between abnormal pre-movement-IHI and the motor deficit implausible. Adding to this, we found no significant cross-sectional correlations between pre-movement-IHI and severity of paresis, assessed by FMA, Strength, or Individuation. Admittedly, given the limited statistical power, we cannot definitively rule out the possibility of an association between pre-movement IHI and a clinical measure. Interestingly though, a recent meta-analysis[27] of 112 TMS studies concluded that "there is no clear evidence for hyper-excitability of the unaffected hemisphere" in either the acute or chronic phases after stroke. Nevertheless, it is important to note that the interpretation of our results, as well as of previous investigations, should be limited to those patients for which it is possible to assess pre-movement-IHI and/or obtain MEPs, i.e. those with mild-to-moderate motor deficits. Therefore, it remains unclear what the interhemispheric-interaction would be for patients with more severe motor deficits.

It would be puzzling, however, if pre-movement-IHI were to be abnormal in the acute period in severe patients given that our mild-to-moderate patients showed improvement from paresis as IHI became worse. Thus, from parsimony, it would seem that the interhemispheric-competition model would not be a satisfactory causal explanation even in patients with severe motor deficits. Unfortunately, methodological limitations prevent us from going beyond this speculation.

The inverse correlation between the emergence of abnormal pre-movement-IHI from the

acute/subacute to chronic stages and recovery of individuation suggests that, rather than any direct causal relationship between them, the development of an abnormal pattern of *ΔIHI* over time might provide an indirect measure of the state of longitudinal recovery. This would mean that the amount of reduction in *ΔIHI* might reflect a less optimal form of reorganization, such as a reliance on contra-lesional corticoreticular projections[28,29], or possibly the consequence of decreasing use of the paretic hand in dexterity-requiring tasks. Both possibilities are consistent with the finding that finger-individuation did not fully recover even at one year after stroke (Fig. 4B). We cannot disambiguate these two possibilities in this study. However, here we show: 1) There is no cross-sectional correlation between pre-movement-IHI and behavior; 2) Behavior gets better as pre-movement-IHI gets worse; 3) The emergence of abnormal pre-movement-IHI is correlated with poor finger-individuation recovery. These results together suggest that the abnormal interhemispheric interaction in the chronic stage might be the consequence of, and a marker for, the state of recovery of the brain rather than the cause of the initial impairment. Therefore, it is questionable that interhemispheric-imbalance should be a therapeutic target.

The results presented here challenge the validity of the interhemispheric-competition recovery model. This is important given that in the past decade, numerous studies have used NIBS in an attempt to down-regulate the contralesional hemisphere to promote recovery: from 2005-2016 there were 45 published clinical trials using cathodal tDCS[25] and 25 trials up to May 2014 using rTMS[26]. The lasting impact of the model is apparent in a recent influential perspective by Di Pino and colleagues[7], in which they introduce a hybrid recovery model that combines vicariation in the ipsilesional-hemisphere with interhemispheric-competition. Of note, our results do not negate the fact that on occasions, NIBS over the ipsi, contra or bilateral hemisphere have shown beneficial effects[3,4]. What our results do indicate, however, is that any

beneficial effect of NIBS is not likely operating via an interhemispheric-inhibition mechanism, at least for patients with mild-to-moderate hemiparesis.

In conclusion, the results reported here cast doubt on the validity of the interhemispheric-competition model. Future investigations using non-invasive brain stimulation, or other interventions, such as peripheral nerve stimulation, to improve recovery following stroke will require alternative mechanistic justification.

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Author contributions

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Potential Conflicts of Interest

Nothing to report.

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Table 1. *Patient characteristics: gender, age (years), handedness, paretic side, initial FMA (Fugl-Meyer upper limb score, maximum = 66), and initial MoCA (Montreal Cognitive Assessment, maximum = 30).*

Patient	Gender	Age at stroke	Handedness	Paretic Side	Initial FMA	Initial MoCA
1	M	57	R	R	48	27
2	M	66	R	L	65	25
3	M	65	R	L	30	25
4	F	66	R	L	60	19
5	F	63	L	L	57	26
6	M	56	R	L	64	24
7	F	64	L	R	20	16
8	F	60	L	R	55	21
9	M	64	L	L	63	25
10	M	24	R	L	35	23
11	F	67	R	R	16	23
12	M	42	L	R	54	25
13	M	35	R	L	4	29
14	M	48	L	L	16	25
15	M	74	R	R	5	25
16	F	80	R	R	9	24
17	F	64	R	L	58	19
18	M	22	R	R	63	27
19	M	84	R	R	30	26
20	M	53	L	R	30	29
21	M	54	R	L	59	21
22	M	58	R	L	61	23

Table 2. *Distribution of assessment time and data obtained. The first two rows are the number of weeks and days post-stroke at each time point of assessment. The following two rows are patient counts with obtained data. The following six categories are counts of missing data for various reasons: MEP count < 9 at early TMS epochs (20 and 50% RT) are likely due to lack of big enough MEP size (>50 μV), whereas those at late TMS epochs (80 and 50% RT) are likely due to TMS pulses occurring during the movement; "No MEP" or "TS > 90 MSO" can sometimes be overlapping with "No reliable movement (index finger abduction)" count in cases of complete plegia; "Other missing" cases include data missing with random reasons: missed the time-window, patient dropped out of the study, patients refused to continue the session, or technical issues during the session. Percentages out of the total N = 21 are presented in parentheses.*

Total N = 21	W1	W4	W12	W24	W52
Number of weeks post stroke	1-2	4-6	12-14	24-26	52-54
Number of days post stroke	12± 3	34±5	93±8	184±12	369±10
Number of patients					
IHI obtained	10 (48%)	13 (62%)	14 (67%)	18 (86%)	16 (76%)
ΔIHI obtained	8 (38%)	11 (52%)	12 (57%)	16 (76%)	15 (71%)
MEP count < 9 (early TMS epochs)	0 (0%)	1 (5%)	1 (5%)	0 (0%)	0 (0%)
MEP count < 9 (late TMS epochs)	2 (10%)	1 (5%)	1 (5%)	2 (10%)	1 (5%)
No MEP	4 (19%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)
TS > 90 MSO	3 (14%)	4 (19%)	2 (10%)	0 (0%)	0 (0%)
No reliable movement	6 (29%)	3 (14%)	2 (10%)	0 (0%)	0 (0%)
Other missing	2 (10%)	0 (0%)	3 (14%)	3 (14%)	5 (24%)

570 ***Table 3.*** *Cross-sectional correlations between release of IHI prior to movement onset (ΔIHI)*

571 *and behavioral measures, FMA, and Strength and Individuation Indices, at acute/subacute and*

572 *chronic stages. Table shows Pearson-r values; parentheses represent the 95% confidence*

573 *interval for each correlation coefficient.*

	FMA	Strength	Individuation
Acute/subacute (W1 – 12)	0.47 [-0.03, 0.78]	0.46 [-0.05, 0.78]	0.22 [-0.31, 0.65]
Chronic (W24 – 52)	0.06 [-0.50, 0.40]	0.16 [-0.32, 0.57]	0.43 [-0.03, 0.74]

574

Table 4. *Other basic TMS measures. Reported here are mean and standard deviations of IHI at rest (IHI_{rest}), CS and TS stimulation intensities for resting and pre-movement-IHI, MEP amplitude in patients for active corticospinal track integrity (aCST) assessed with 100% MSO, TS at 95 and 80% of RT, and resting motor threshold (rMT) in patients and controls. Independent samples t-tests were done between patients and controls for IHI_{rest} and CS and TS intensities at each time point. MEP amplitudes were compared between aCST and TS at each time point among patients. Comparison of rMT were done between paretic vs. non-paretic hands in patients, and dominant vs. non-dominant hands in healthy controls.*

	Mean (SD)					T-tests *t*-value (*p*-value)				
Week	1	4	12	24	52	1	4	12	24	52
IHI_{rest}			IHIR					Patient vs. Control		
Patient	0.69 (0.20)	0.67 (0.19)	0.81 (0.16)	0.79 (0.20)	0.73 (0.25)	0.81 (0.44)	0.60 (0.56)	0.11 (0.56)	0.11 (0.91)	0.35 (0.73)
Control	0.59 (0.26)	0.73 (0.29)	0.73 (0.44)	0.78 (0.32)	0.70 (0.22)					
			CS Stimulus Intensity (% MSO)							
Patient	57 (17)	57 (15)	53 (13)	55 (15)	55 (16)	0.15 (0.88)	1.21 (0.24)	0.65 (0.53)	0.20 (0.84)	0.08 (0.94)
Control	58 (8)	49 (10)	49 (4)	56 (14)	56 (15)					
			TS Stimulus Intensity (% MSO)							
Patient	57 (19)	59 (20)	60 (16)	63 (18)	57 (17)	0.19 (0.85)	0.61 (0.55)	0.79 (0.44)	0.01 (0.99)	0.40 (0.69)
Control	59 (9)	54 (7)	54 (8)	63 (11)	60 (12)					
$IHI_{premove}$			CS Stimulus Intensity (% MSO)							
Patient	56 (17)	57 (16)	55 (18)	58 (16)	54 (14)	0 (1.00)	1.12 (0.28)	0.70 (0.49)	0.23 (0.82)	0.30 (0.77)
Control	56 (8)	50 (10)	49 (4)	56 (14)	56 (15)					
			TS Stimulus Intensity (% MSO)							
Patient	55 (18)	52 (16)	60 (19)	60 (18)	56 (14)	0.35 (0.73)	0.60 (0.55)	1.12 (0.28)	0.32 (0.75)	0.50 (0.62)
Control	52 (7)	48 (6)	50 (6)	58 (9)	53 (12)					
			MEP Amplitude in Patient (mV)					aCST vs. TS		
aCST	2.89 (1.36)	3.71 (1.99)	3.27 (1.80)	2.78 (1.53)	3.27 (2.12)					
TS at 95% RT	2.22 (1.46)	2.51 (1.07)	2.00 (1.28)	1.68 (1.32)	1.81 (0.99)	1.05 (0.31)	1.91 (0.07)	2.13 (0.04*)	2.28 (0.03*)	2.48 (0.02*)
TS at 80% RT	1.81 (1.06)	1.82 (0.91)	1.64 (1.26)	1.33 (1.23)	1.55 (0.81)	1.97 (0.06)	3.11 (0.005*)	2.74 (0.01*)	3.10 (0.004*)	3.02 (0.005*)
Patient			rMT					Paretic vs. non-paretic		
Paretic	62 (24)	54 (21)	50 (13)	47 (14)	46 (13)	3.34 (0.002*)	2.74 (0.009*)	2.72 (0.01*)	1.70 (0.10)	1.48 (0.15)
Non-paretic	42 (11)	40 (9)	40 (9)	40 (10)	40 (10)					
Control								Paretic vs. control		
Dominant	47 (7)	46 (8)	48 (9)	45 (8)	45 (7)	1.95 (0.06)	1.20 (0.24)	0.51 (0.62)	0.42 (0.68)	0.25 (0.81)
Non-dominant	43 (9)	42 (7)	41 (6)	42 (7)	40 (6)	2.43 (0.02*)	1.87 (0.07)	2.08 (0.046*)	1.19 (0.24)	1.42 (0.167)

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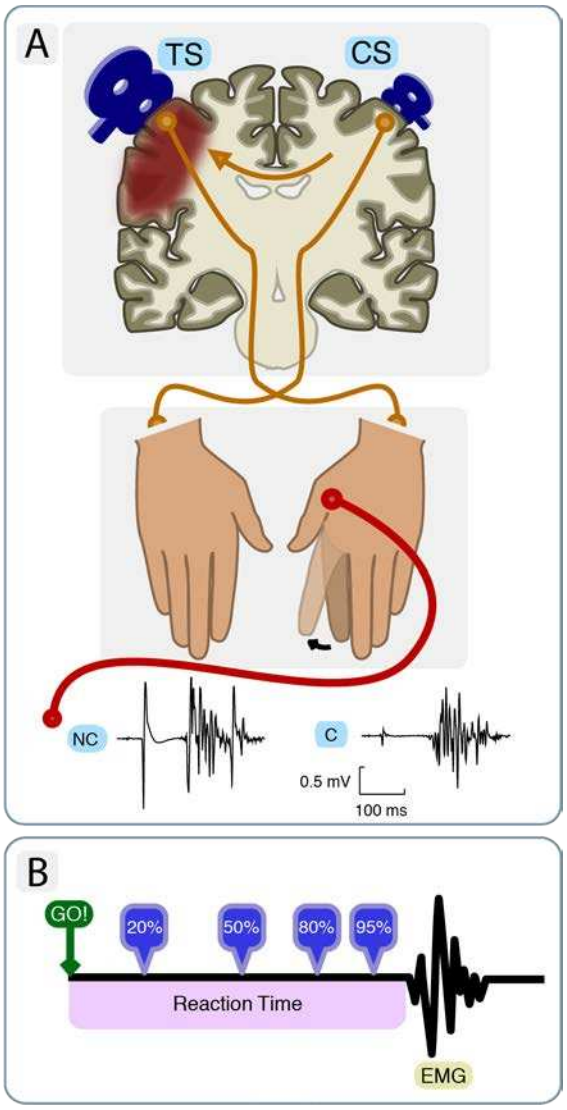
Figure 1. *Schematic illustration of the pre-movement Interhemispheric Inhibition (IHI) paradigm. (**A**) A Test Stimulus (TS) was delivered over the lesioned hemisphere, and a Conditioning Stimulus (CS) was applied over the intact hemisphere prior to index finger abduction of the paretic hand (or right hand in healthy age-matched controls). In non-conditioned (NC) trials only the TS was delivered, while in conditioned (C) trials the CS preceded TS by 10ms. EMG signals were recorded from the first dorsal interosseous muscle (FDI) of the moving hand; (**B**) TMS pulses were delivered at four timing epochs relative to the individual's mean reaction time, estimated from a simple-reaction task.*

Figure 2. *Lesion distribution of patients (N = 21). Averaged lesion distribution mapped to JHU-MNI space[30], with lesion flipped to one hemisphere. Color bar indicates patient count.*

Figure 3. *Release of IHI prior to movement onset. (**A**) IHI curves for a representative patient and a healthy control. These exemplar IHI profiles illustrate the normal release of IHI in patients at the acute/subacute stage, comparable to control subjects, and the lack of normal release of IHI during the chronic period; (**B**) Overall mean IHI curves for healthy controls. Since there were no differences over time in pre-movement-IHI in controls (mixed-effects model with Week and TMS-Timing as fixed factors showed no significant effect of Week, $\chi^2 = 0.067$, $p = 0.80$, but significant main effect of TMS-Timing, $\chi^2 = 22.28$, $p < 0.001$), we averaged control data across weeks. (**C**) IHI curves for each time point over the one-year period for patients; (**D**) Evolution of ΔIHI for patients and controls over the one-year period. Patient showed close to control level of ΔIHI in the actue/subacute periods (W1-12), but their ΔIHI's became abnormal at the chronic stage. Shaded plots in grey and red are sensitivity analysis with two imputation schemes with MAR and informed-missingness cases respectively, where missing not at random (MNAR) cases are imputed with 1000 samples from $N\sim(\mu_{(t,patient)}, \sigma_{(t,patient)})$ or $N\sim(0, \sigma_{patient})$.*

609 *$\mu_{(t,patient)}$ and $\sigma_{(t,patient)}$ are estimated from patients data at each time point and $\sigma_{patient}$ is estimated*
610 *from all patients' data. (**E**) Distribution of p-values from sensitivity analysis with multiple*
611 *imputation for the MAR and informed-missingness cases. (**F**) Change of IHI level at different*
612 *movement preparation epochs in patients from the acute/subacute to chronic stage after stroke.*
613 *There was a significant interaction of $IHI_{EARLY\text{-}EPOCH}$ vs. $IHI_{LATE\text{-}EPOCH}$ or acute/subacute and*
614 *chronic stages ($\chi^2 = 4.34$, $p = 0.037$), but no differences when comparing across acute/subacute*
615 *vs. chronic stages for $IHI_{EARLY\text{-}EPOCH}$ ($t(14) = 0.75$, $p = 0.47$) or $IHI_{LATE\text{-}EPOCH}$ ($t(14) = 1.69$, $p =$*
616 *0.11). Means and variances in all plots were estimated by mixed-models.*
617 ***Figure 4**. Recovery curves for behavior measures of hand function over one-year period, from*
618 *week 1-52. (**A**) Strength Indices, (**B**) Individuation Indices, (C) FMA. Means and variances are*
619 *estimated by mixed-model.*
620 ***Figure 5.** Correlations between the reduction of pre-movement-IHI (ΔIHI) from acute/subacute*
621 *to chronic stages and the amount of behavioral recovery: (**A**) Strength, (**B**) Individuation. x- and*
622 *y-axes are the mean differences between chronic and acute/subacute behavior measures and Δ*
623 *IHI, respectively.*
624 ***Figure 6.** Other behavioral and physiological measures in pre-movement experiments. Reaction*
625 *time (RT) for patients (**A**) and controls (**B**) at different TMS timing during movement preparation*
626 *across the one-year period. RTs for controls were overall faster than patients. Background EMG*
627 *for patients (**C**) was overall lower than that in controls (**D**), but was at a similar level for*
628 *conditioned vs. non-conditioned TMS stimulation.*
629



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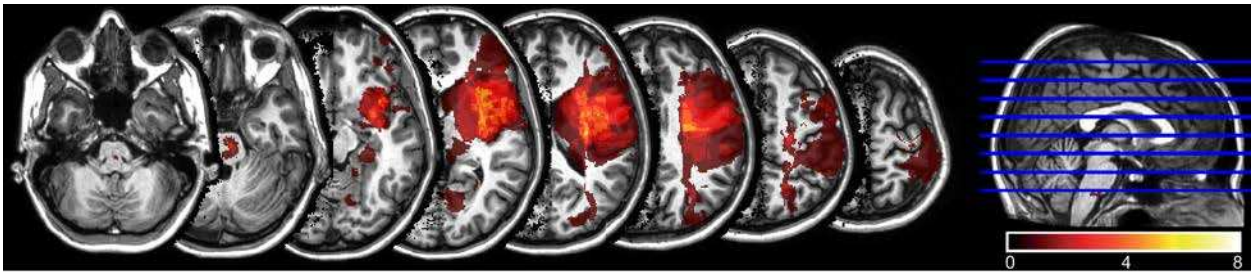
632 

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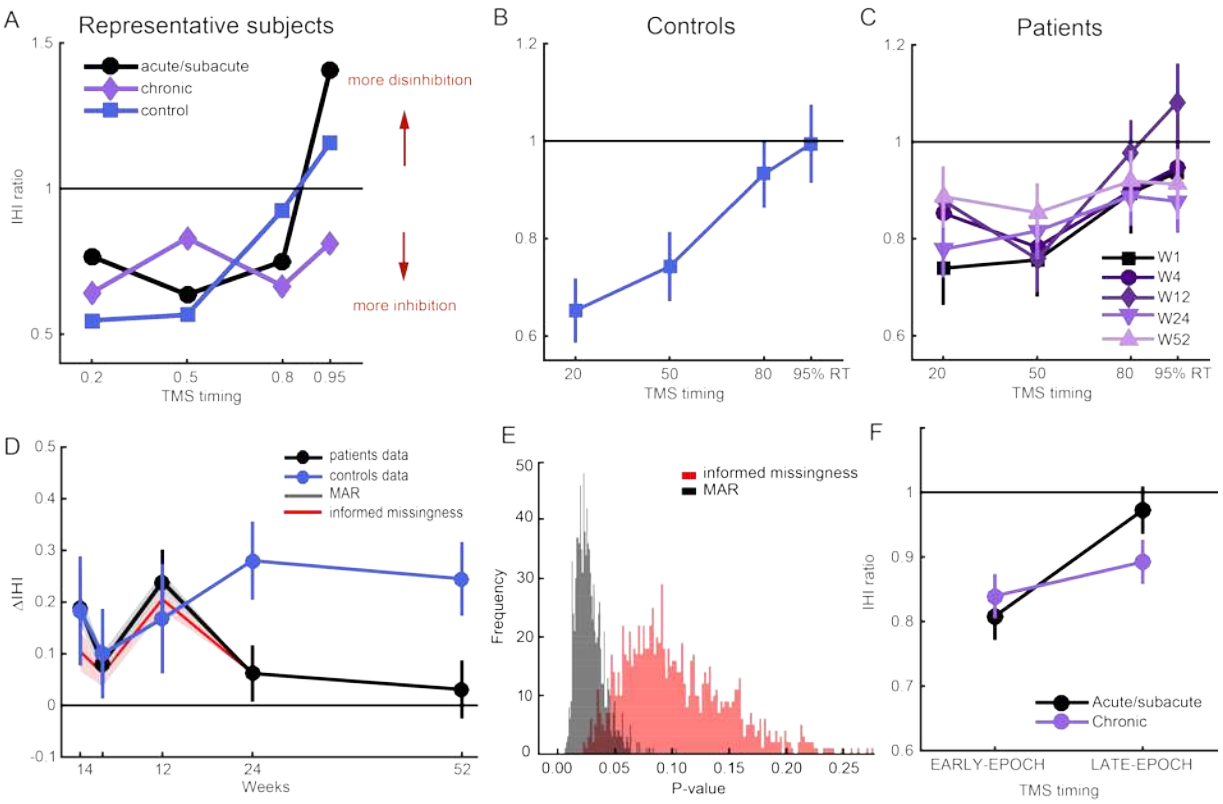
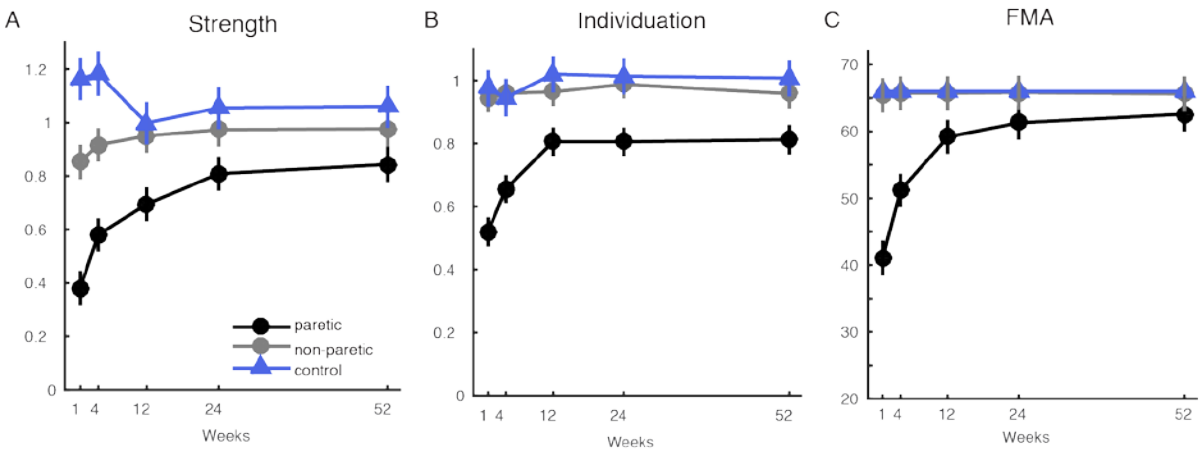

A
Representative subjects
acute/subacute
chronic
control
more disinhibition
more inhibition
IHI ratio
TMS timing
B
Controls
TMS timing
C
Patients
W1
W4
W12
W24
W52
TMS timing
D
patients data
controls data
MAR
informed missingness
ΔIHI
Weeks
E
informed missingness
MAR
Frequency
P-value
F
IHI ratio
Acute/subacute
Chronic
EARLY-EPOCH
LATE-EPOCH
TMS timing

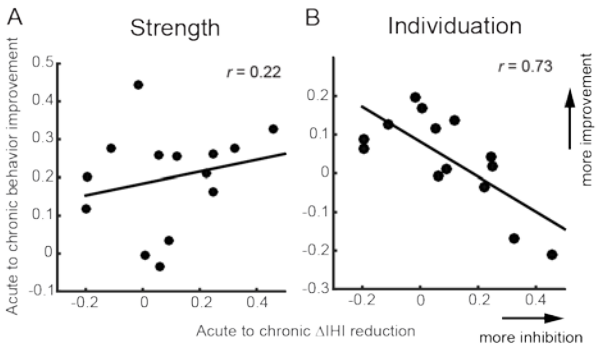
634

635


A
Strength
1.2
1
0.8
0.6
0.4
0.2
0
paretic
non-paretic
control
1 4 12 24 52
Weeks
B
Individuation
1
0.8
0.6
0.4
0.2
0
1 4 12 24 52
Weeks
C
FMA
70
60
50
40
30
20
1 4 12 24 52
Weeks

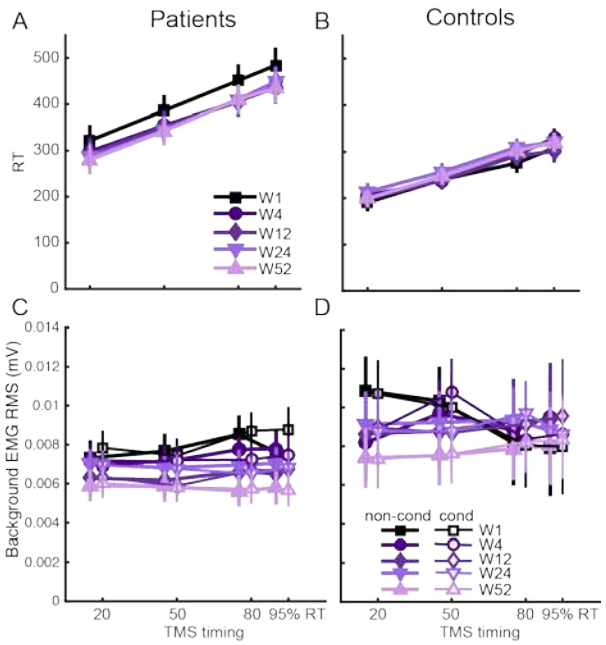
636

637


A
Strength
r = 0.22
B
Individuation
r = 0.73
more improvement
Acute to chronic behavior improvement
Acute to chronic ΔIHI reduction
more inhibition

638

639


A
Patients
B
Controls
RT
500
400
300
200
100
0
W1
W4
W12
W24
W52
C
D
Background EMG RMS (mV)
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
non-cond
cond
20
50
80
95% RT
TMS timing

640